PATENT SPECIFICATION

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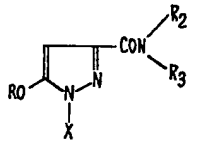
(19)

(54) PYRAZOLES AND PROCESS FOR THEIR PREPARATION

(71) We, MARUKO SEIYAKU CO., LTD., a Japanese Company, of No. 3, 2-Chome, Kodama-Cho, Nishi-Ku, Nagoya-Shi, Aichi, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel pyrazole derivatives and, more particularly, this invention relates to novel pyrazole derivatives represented by the formula:



(I)

wherein R represents an alkyl group, X represents either a mono- or di-substituted phenyl group wherein the substituents may be the same or different and each represents an alkyl group, an alkoxy group, a trifluoromethyl group, a nitro group, an amino group or a halogen atom, or a halogen substituted or unsubstituted benzyl group, and either R_2 represents a hydrogen atom or an alkyl group and R_3 represents a hydrogen atom, a hydroxyalkyl group, an alkyl group or a substituted aminoalkyl group, or R_2 and R_3 form, when taken together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic group which may contain one oxygen as a hetero atom. The invention also relates to a process for preparing the pyrazole derivatives represented by the formula (I) above.

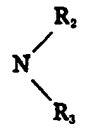
The pyrazole derivatives according to the present invention exhibit potent analgesic and anti-inflammatory activities and, therefore, are useful as pharmaceuticals for treating and alleviating various inflammatory conditions in animals and humans. Accordingly the invention also includes pharmaceutical compositions comprising a pyrazole as described above and a pharmaceutically acceptable carrier.

An object of the present invention is to provide novel pyrazole derivatives which are useful as analgesics and anti-inflammatory agents.

Another object of the present invention is to provide a process for preparing such novel pyrazole derivatives.

The terms "alkyl" and "alkoxy" used throughout the specification mean an alkyl group having 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl and tert-butyl groups and the corresponding alkoxy groups.

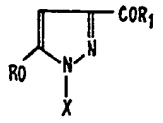
The term "5- or 6-membered heterocyclic group" used for the group



in the above formula (I) includes a pyrrolidino group, a piperidino group, a substituted piperazino group wherein the substituent is an alkyl group having 1 to 4 carbon atom such as 4-methylpiperazino, or a morpholino group.

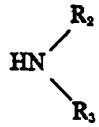
The pyrazole derivatives of the present invention represented by the formula (I) above can easily be prepared by reacting a 5-

alkoxypyrazole represented by the formula:



(II)

wherein R and X are as defined above, and R_1 represents an alkoxy group (such as a methoxy or ethoxy group), a hydroxy group or a halogen atom (such as a chlorine or bromine atom), with an amine represented by the formula:



(III)

wherein R_2 and R_3 are as defined above. The process of this invention, i.e., an amidation of the 5-alkoxypyrazole (II), proceeds easily by reacting the 5-alkoxypyrazole with an amine corresponding to the amino group in the desired pyrazole derivative (I) in an inert organic solvent or in the presence of an excess amount of the amine which serves as both a solvent and a reactant. Generally, the reaction can be carried out in an inert organic solvent or in the presence of an excess of an amine (III) at a temperature of from 0° C to 80° C using at least an equimolar amount of the amine relative to a 5-alkoxypyrazole for a period of from 20 minutes to 16 hours.

The reaction conditions employed in the process of this invention somewhat vary depending upon the type of the starting material, in particular, the type of the substituent R_1 in the 5-alkoxypyrazole (II) reaction.

When R_1 represents an alkoxy group, i.e., the substituent at 3-position of the starting material (II) represents an alkyl ester —$COOR_1$, the amidation can conveniently be carried out in an organic solvent, such as alkanols having 1 to 4 carbon atoms (for example, methanol or ethanol) or benzene, using 1 to 5 moles, preferably 2 to 5 moles of an amine per 1 mole of the 5-alkoxypyrazole, while heat-refluxing the reaction mixture, generally at a temperature of from 60 to 80° C, for a period of from 1 to 5 hours. A well-known condensing agent such as aluminum isopropoxide or sodium amide can be used in the amidation reaction to ensure a smooth reaction but the use of such a condensing agent is not essential. Alternatively, when the amine of the formula (III) has a low boiling point, e.g., below 50° C under atmospheric pressure, the reaction is advantageously carried out in a sealed reaction vessel under pressure, for example, in an autoclave under an autogenous pressure.

When R_1 represents an —OH group, i.e., the substituent at the 3-position of the starting material (II) represents a carboxy group —COOH, the amidation can advantageously be carried out in an inert organic solvent, such as methylene chloride or chloroform, optionally in the presence of a dehydrating agent, for example, N,N'-dicyclohexylcarbodiimide, at a temperature of from ice-cooling temperature (about 10° C) to room temperature (about 25° C) for a period of from 3 to 16 hours, preferably 8 to 16 hours. In this reaction, the amine can advantageously be used from 1 to 2 moles per 1 mole of the 5-alkoxypyrazole (II).

When R_1 represents a halogen atom, i.e., the substituent at 3-position of the starting material (II) represents an acid halide group, the amidation can easily be carried out by reacting an acid halide (II) with an amine (III) in an inert organic solvent, such as ethyl ether, chloroform, benzene, pyridine or triethylamine, at a temperature of from ice-cooling temperature to room temperature for a period of from 20 minutes to 2 hours, preferably from 30 minutes to 1 hour. In this reaction, the amine reactant can advantageously be used in an excess amount, for example, from 2 to 5 molar excess so as to serve as a reactant as well as a reaction solvent.

The present invention also includes the pharmaceutically acceptable acid addition salts of the pyrazole derivatives of the formula (I). These acid addition salts can be prepared from the free base compound (I) by conventional procedures, for example, by introducing hydrogen chloride gas into a solution of the free base compound in an organic solvent such as methanol to form the corresponding hydrochloride salt of the pyrazole derivatives. Typical examples of the pharmaceutically acceptable acid addition salts of the pyrazole derivatives (I) are hydrochlorides, sulfates, phosphates, oxalates, fumarates, maleates and tartrates.

As described previously, the pyrazole derivatives represented by the above formula (I) exhibit potent analgesic and anti-inflammatory activities. For example, 1-(p-tolyl)-3-N,N - dimethylcarbamoyl - 5 - methoxypyrazole (Compound A), 1 - (m - trifluoromethylphenyl) - 3 - N,N - dimethylcarbamoyl - 5 - n - butoxypyrazole (Compound B), 1 - (m - chlorophenyl) - 3 - N,N-dimethylcarbamoyl - 5 - methoxypyrazole (Compound C), 1 - (m - chlorophenyl)-3 - carbamoyl - 5 - methoxypyrazole (Compound D) and 1 - (p - chlorobenzyl)-3 - N - methylcarbamoyl - 5 - methoxypyrazole (E) exhibit excellent analgesic activity as determined by the acetic acid stretching method and the pressure-stimulation method described below.

Acetic Acid Stretching Method

Each of the test compounds (Compounds A to E) was administered orally to ddN male mice weighing 17 to 20 g (5 to 7 mice per group) and 30 minutes after administration, a 0.7% aqueous solution of acetic acid was administered intraperitoneally to the mice in a dose of 0.1 ml per 10 g of the body weight. The number of stretching of the mice for a period of 5 minutes was then counted 15 and 30 minutes after the administration of the aqueous acetic acid and compared with the number of stretching in the control group which received only the aqueous acetic acid to determine the percent inhibitory of the test compounds. In this experiment, Compounds A to E were found to have a stretching inhibitory activity (analgesic activity) of 2.0, 4.0, 3.4, 2.2 and 1.6 times, respectively, higher than that of aminopyrine.

Pressure-Stimulation Method

Each of the test compounds (Compounds A to E) was administered orally to ddN male mice weighing 18 to 20 g (8 to 10 mice per group), and pressure was applied to the tail using a pressure-stimulation apparatus (Takagi et al apparatus). The reaction of the mice, i.e., turning of the head toward the stimulated portion and biting behavior, was observed as the criterion and the pain threshold was determined. In this experiment, Compounds A to E were found to have an analgesic activity of 1.8, 1.6, 2.5, 2.0 and 1.8 times, respectively, higher than that of aminopyrine.

The compounds of this invention also possess an excellent anti-inflammatory activity as determined by the well-established carrageenin-induced edema inhibitory activity described below.

Carrageenin-Induced Edema Inhibitory Activity

Each of the test compounds (Compounds A to E) was administered orally to Wister male rats weighing about 150 g (7 to 8 rats per group) and 30 minutes after the administration of the test compound, 0.1 ml of a 1% aqueous solution of carrageenin was administered subcutaneously to a hind paw of the rats. Thereafter, the volume of the paw was measured at an interval of 1 hour to determine the swelling ratio of the paw relative to the volume of the same paw before administration of the aqueous carrageenin. The edema inhibitory activity was calculated by comparing the swelling ratio in the control group which received only the test compounds. In this experiment, Compounds A to E were found to have an edema inhibitory activity of 1.8, 2.0, 3.5, 2.2 and 1.9 times, respectively, higher than that of aminopyrine.

The acute toxicity of the test compounds was also determined in rats by oral administration in the standard method and found to be 1620 mg/kg, 760 mg/kg, 950 mg/kg, 930 mg/kg and 540 mg/kg, respectively in terms of a 50% lethal dose (LD_{50}).

The present invention is further illustrated by the following Examples, but they are not to be construed as limiting the scope of this invention.

Example 1.

1 - (m - Trifluoromethylphenyl) - 3 - N,N-dimethylcarbamoyl - 5 - n - butoxypyrazole.

34.7 g of 1 - (m - trifluoromethylphenyl) - 5 - n - butoxypyrazole - 3 - yl carbonyl chloride was dissolved in 150 ml of ethyl ether, and to the resulting solution was added dropwise 50 ml of a solution containing 11 g of dimethylamine in ethyl ether while cooling the mixture to a temperature of 10° C with stirring. After allowing to stand for 1 hour, the reaction mixture was washed successively with 5% hydrochloric acid, 5% aqueous sodium carbonate and water. The ethereal layer was separated and dried over anhydrous sodium sulfate. The solvent (ethyl ether) was then removed by distillation and the resulting residue was recrystallized from n-pentane to give 29.8 g (83.9% yield) of 1-(m - trifluoromethylphenyl) - 3 - N,N - dimethylcarbamoyl - 5 - n - butoxypyrazole as colorless prisms having a melting point of 66 to 68° C.

Analysis

Calcd. for $C_{17}H_{20}O_2N_3F_3$ (Molecular Weight: 355.4):
C, 57.46; H, 5.67; N, 11.82.
Found: C, 57.62; H, 5.75; N, 11.84.

Example 2.

1 - (p - Tolyl) - N,N - dimethylcarbamoyl-5 - methoxypyrazole.

23.2 g of 1 - (p - tolyl) - 3 - carboxy-5 - methoxypyrazole was dissolved in 100 ml of chloroform, and to the resulting solution was added a solution containing 4 g of dimethylamine in 20 ml of chloroform while cooling the mixture to a temperature of 5 to 10° C with stirring. 50 ml of a solution of 10 g of N,N-dicyclohexylcarbodiimide in chloroform was then added dropwise to the resulting mixture and, after completion of the addition, the mixture was allowed to cool to room temperature followed by stirring for 7 hours. The reaction mixture was then made acidic with acetic acid and the precipitated crystals were then removed by filtration. The solvent was removed from the filtrate by distillation and the resulting residue was washed successively with 5% aqueous sodium hydroxide and water. Recrystallization from ethyl ether-petroleum ether gave 12 g (46.3% yield) of 1 - (p - tolyl) - 3 - N,N - dimethylcarbamoyl - 5 - methoxypyrazole as colorless prisms having a melting point of 120—121° C.

Analysis
Calcd. for $C_{14}H_{17}O_2N_3$ (Molecular Weight: 259.3)
C, 64.85; H, 6.61; N, 16.20.
Found: C, 65.06; H, 6.54; N, 16.07.

The combined washings obtained above, i.e., the 5% aqueous sodium hydroxide and water, was made acidic with hydrochloric acid and the precipitated crystals were separated by filtration to recover 10.3 g (44.4% yield) of the unreacted starting material, 1-(p-tolyl)-3-carboxy-5-methoxypyrazole.

Example 3.

1 - (p - Chlorobenzyl) - 3 - carbamoyl-5 - n - butoxypyrazole.

A mixture consisting of 6.7 g of 1-(p-chlorobenzyl) - 3 - ethoxycarbonyl - 5 - n-butoxypyrazole, 30 ml of a 28% aqueous ammonia solution and 30 ml of methanol was placed in an autoclave and heated at a temperature of 60° C for 2 hours. After completion of the reaction, the solvent was removed by distillation and the residue was recrystallized from methanol-petroleum ether to give 5.3 g (86.2% yield) of 1-(p-chlorobenzyl)-3-carbamoyl - 5 - n - butoxypyrazole as colorless needles having a melting point of 137—138° C.

Analysis
Calcd. for $C_{15}H_{18}O_2N_3Cl$ (Molecular Weight: 307.8):
C, 58.54; H, 5.89; N, 13.65.
Found: C, 58.66; H, 5.86; N, 13.62.

Example 4.

1 - (p - Chlorobenzyl) - 3 - (4' - methylpiperazinyl) - carbonyl - 5 - methoxypyrazole hydrochloride.

5.7 g of 1 - (p - chlorobenzyl) - 5-methoxypyrazol-3-yl carbonyl chloride was dissolved in 60 ml of benzene, and to the resulting solution was added dropwise 3 g of N-methylpiperazine with stirring. After allowing the reaction mixture to stand for 20 minutes, the mixture was washed well successively with 10% aqueous sodium hydroxide and water. The benzene layer was then separated and dried, and the benzene was then removed by distillation. The resulting residue was dissolved in methanol and hydrogen chloride gas was introduced into the methanolic solution. The methanol was then removed by distillation and the resulting crystals were recrystallized from methanol-ethyl ether to give 5.4 g (70.1% yield) of 1-(p-chlorobenzyl) - 3 - (4' - methylpiperazinyl) - carbonyl - 5 - methoxypyrazole hydrochloride as a colorless crystalline powder having a melting point of 223 to 225° C (with decomposition).

Analysis
Calcd. for $C_{17}H_{21}O_2N_4Cl \cdot HCl$ (Molecular Weight: 385.3):
C, 53.00; H, 5.76; N, 14.54.
Found: C, 52.94; H, 5.83; N, 14.41.

Example 5.

1 - (p - Chlorophenyl) - 3 - N,N - dimethylcarbamoyl - 5 - n - butoxypyrazole.

A mixture consisting of 16.1 g of 1-(p-chlorophenyl) - 3 - ethoxycarbonyl - 5 - n-butoxypyrazole, 4 g of dimethylamine and 200 ml of ethanol was placed in an autoclave and heated at a temperature of from 70 to 80° C for 4 hours with stirring. After completion of the reaction, the solvent was removed by distillation, and the residue was washed successively with 5% hydrochloric acid and water. Recrystallization from ethyl ether-petroleum ether gave 11.8 g (73.3% yield) of 1 - (p - chlorophenyl) - 3 - N,N-dimethylcarbamoyl - 5 - n - butoxypyrazole as colorless needles having a melting point of 94 to 95° C.

Analysis
Calcd. for $C_{16}H_{20}O_2N_3Cl$ (Molecular Weight: 321.8):
C, 59.72; H, 6.26; N, 13.06.
Found: C, 59.85; H, 6.31; N, 12.98.

Example 6.

1 - (p - Tolyl) - 3 - N,N - dimethylcarbamoyl - 5 - n - butoxypyrazole.

29.3 g of 1 - (p - tolyl) - 5 - n - butoxypyrazole - 3 - yl carbonyl chloride was dissolved in 150 ml of benzene, and to the resulting solution was added dropwise a solution of 11 g of dimethylamine in 50 ml of benzene while maintaining the mixture at a temperature of from 10 to 15° C with stirring. The reaction mixture was then worked up in the same manner as described in Example 1 and the product thus obtained was recrystallized from ethyl ether-petroleum ether to give 24.1 g (80.0% yield) of 1-(p-tolyl)-3-N,N-dimethylcarbamoyl - 5 - n - butoxypyrazole as colorless plates having a melting point of 99—100° C.

Analysis
Calcd. for $C_{17}H_{23}O_2N_3$ (Molecular Weight: 301.4):
C, 67.75; H, 7.69; N, 13.94.
Found: C, 67.78; H, 7.78; N, 13.81.

Example 7.

1 - (p - Chlorophenyl) - 3 - N,N - dimethylcarbamoyl - 5 - methoxypyrazole.

25.3 g of 1 - (p - chlorophenyl) - 3-carboxy - 5 - methoxypyrazole was dissolved in 100 ml of methylene chloride, and to the resulting solution was added dropwise a solution of 4 g of dimethylamine in 20 ml of

methylene chloride while maintaining the mixture at a temperature of from 5 to 10° C with stirring. A solution of 10 g of N,N8-dicyclohexylcarbodiimide in 50 ml of methylene chloride was then added dropwise to the mixture. The reaction mixture was then worked up in the same manner as described in Example 2 and the product thus obtained was recrystallized from ethyl ether-petroleum ether to give 12.7 g (45.4% yield) of 1-(p-chlorophenyl) - 3 - N,N - dimethylcarbamoyl-5-methoxypyrazole as colorless prisms having a melting point of 116—118° C.

Analysis

Calcd. for $C_{13}H_{14}O_2N_3Cl$ (Molecular Weight: 279.7):
C, 55.82; H, 5.04; N, 15.02.
Found: C, 55.75; H, 5.06; N, 15.02

In the same manner as described in the proceeding Examples, the following compounds were also prepared from a 5-alkoxypyrazole (II) and an amine (III).

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. (Found) C	H	N
8	1-(p-tolyl-3-N,N-dimethylcarbamoyl-5-isopropoxypyrazole	Colorless Prisms	Ethyl ether-petroleum ether	90–91	$C_{16}H_{21}O_2N_3$ (287.4)	66.88 (66.78	7.34 7.45	14.62 14.68)
9	1-(p-chlorophenyl)-3-N,N-dimethyl-carbamoyl-5-ethoxypyrazole	Colorless Needles	Ethyl ether-petroleum ether	107–108	$C_{14}H_{16}O_2N_3Cl$ (293.8)	57.24 (57.20	5.49 5.50	14.30 14.14)
10	1-(p-chlorophenyl)-3-N,N-dimethyl-carbamoyl-5-n-propoxypyrazole	Colorless Prisms	Ethyl ether-petroleum ether	83–84	$C_{15}H_{18}O_2N_3Cl$ (307.8)	58.54 (58.71	5.89 5.95	13.65 13.66)
11	1-(m-chlorophenyl)-3-N,N-dimethyl-carbamoyl-5-methoxypyrazole	Colorless Prisms	Ethyl ether	98–99	$C_{13}H_{14}O_2N_3Cl$ (279.7)	55.82 (56.01	5.04 5.01	15.02 14.94)
12	1-(m-trifluoromethylphenyl)-3-N,N-dimethylcarbamoyl-5-n-propoxy-pyrazole	Colorless Prisms	Petroleum benzine	83–84	$C_{16}H_{18}O_2N_3F_3$ (341.3)	56.30 (56.17	5.32 5.33	12.31 12.33)
13	1-(m-trifluoromethylphenyl)-3-N,N-dimethylcarbamoyl-5-ethoxy-pyrazole	Colorless Needles	Petroleum benzine	83–84	$C_{15}H_{16}O_2N_3F_3$ 327.3	55.05 (55.21	4.93 4.98	12.84 12.83)
14	1-(m-trifluoromethylphenyl)-3-N,N-dimethylcarbamoyl-5-methoxy-pyrazole	Colorless Needles	Benzene-petroleum ether	116–117	$C_{14}H_{14}O_2N_3F_3$ (313.3)	53.68 (53.75	4.50 4.41	13.41 13.20)
15	1-(p-tolyl)-3-morpholinocarbonyl-5-methoxypyrazole	Colorless Oil	—	b.p. 130–131/ 2 mmHg	$C_{16}H_{19}O_3N_3$ (301.3)	63.77 (63.93	6.36 6.45	13.94 13.76)
16	1-(p-chlorophenyl)-3-(4'-methyl-piperazinyl)-carbonyl-5-methoxy-pyrazole	Colorless Needles	Ethanol-Petroleum ether-Ethyl ether	116–117	$C_{16}H_{19}O_2N_4Cl$ (334.8)	57.40 (57.34	5.72 5.79	16.73 16.52)

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. (Found) C	H	N
17	1-(m-chlorophenyl)-3-N,N-diisopropylcarbamoyl-5-methoxypyrazole	Colorless Prisms	Ethyl ether-Petroleum ether	102–103	$C_{17}H_{22}O_2N_3Cl$ (335.8)	60.80 (60.86	6.60 6.53	12.51 12.37)
18	1-(m-chlorophenyl)-3-morpholinocarbonyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	73–74	$C_{15}H_{16}O_3N_3Cl$ (321.8)	55.99 (56.06	5.01 4.94	13.06 13.02)
19	1-(m-chlorophenyl)-3-(4'-methylpiperazinyl)-carbonyl-5-methoxypyrazole	Colorless Crystalline Powder	Ethyl ether-Petroleum ether	76–77	$C_{16}H_{19}O_2N_4Cl$ (334.8)	57.40 (57.36	5.72 5.64	16.73 16.64)
20	1-(p-chlorophenyl)-3-N,N-diisopropylcarbamoyl-5-methoxypyrazole	Colorless Plates	Methanol-Petroleum ether	126–127	$C_{17}H_{22}O_2N_3Cl$ (335.8)	60.80 (60.68	6.60 6.61	12.51 12.59)
21	1-(p-tolyl)-3-N,N-diisopropylcarbamoyl-5-methoxypyrazole	Colorless Plates	Ethanol-Petroleum ether	95–96	$C_{17}H_{25}O_2N_3$ (303.4)	67.30 (67.47	8.31 8.27	13.85 13.72)
22	1-(p-chlorophenyl)-3-morpholinocarbonyl)-5-methoxypyrazole	Colorless Needles	Ethanol-Petroleum ether	109–110	$C_{1}H_{16}O_3N_3Cl$ (309.8)	54.29 (54.16	5.21 5.21	13.57 13.55)
23	1-(p-chlorophenyl)-3-(pyrrolidin-1-yl)-carbonyl-5-methoxypyrazole	Colorless Needles	Ethanol-Petroleum ether	156–158	$C_{15}H_{16}O_2N_3Cl$ (305.8)	58.92 (58.98	5.27 5.34	13.74 13.58)
24	1-(p-chlorophenyl)-3-N-methylcarbamoyl-5-methoxypyrazole	Colorless Crystalline Powder	Ethanol-Petroleum ether	121–122	$C_{12}H_{12}O_2N_3Cl$ (265.7)	54.25 (54.25	4.55 4.44	15.81 15.94)

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. (Found) C	H	N
25	1-(p-chlorophenyl)-3-N-n-butylcarbamoyl-5-methoxypyrazole	Colorless Prisms	Ethanol-Petroleum ether	53–54	$C_{15}H_{18}O_2N_3Cl$ (307.8)	58.54 (58.69	5.89 5.86	13.65 13.51)
26	1-(m-chlorophenyl)-3-N-methylcarbamoyl-5-methoxypyrazole	Colorless Crystalline Powder	Ethyl ether-Petroleum ether	136–137	$C_{12}H_{12}O_2N_3Cl$ (265.7)	54.25 (54.42	4.55 4.61	15.81 15.72)
27	1-(m-chlorophenyl)-3-N-sec-butylcarbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	96–97	$C_{15}H_{18}O_2N_3Cl$ (307.8)	58.54 (58.67	5.89 5.93	13.65 13.50)
28	1-(m-chlorophenyl)-3-(pyrrolidin-1-yl)-carbonyl-5-methoxypyrazole	Colorless Prisms	Ethyl ether-Petroleum ether	111–112	$C_{15}H_{16}O_2N_3Cl$ (305.8)	58.92 (59.13	5.27 5.30	13.74 13.71)
29	1-(o-chlorophenyl)-3-N,N-dimethylcarbamoyl-5-methoxypyrazole	Colorless Plates	Methanol-Petroleum ether	142–144	$C_{13}H_{14}O_2N_3Cl$ (279.7)	55.82 (55.96	5.04 5.08	15.02 15.01)
30	1-(m-chlorophenyl)-3-N-methylcarbamoyl-5-n-butoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	77–78	$C_{15}H_{18}O_2N_3Cl$ (307.8)	58.54 (58.51	5.89 5.93	13.65 13.52)
31	1-(m-chlorophenyl)-3-N,N-dimethylcarbamoyl-5-n-butoxypyrazole	Colorless Plates	Ethyl ether-Petroleum ether	63–64	$C_{16}H_{20}O_2N_3Cl$ (321.8)	59.72 (59.86	6.26 6.24	13.06 12.89)
32	1-(m-chlorophenyl)-3-(pyrrolidin-1-yl)-carbonyl-5-n-butoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	81–82	$C_{18}H_{22}O_2N_3Cl$ (347.8)	62.15 (62.32	6.38 6.40	12.08 12.12)
33	1-(m-chlorophenyl)-3-carbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl acetate	150–152	$C_{11}H_{10}O_2N_3Cl$ (251.7)	52.50 (52.57	4.01 4.03	16.70 16.61)

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. (Found) C	H	N
34	1-(m-chlorophenyl)-3-N-ethylcarbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum benzine	85–86	$C_{13}H_{14}O_2N_3Cl$ (279.7)	51.53 (51.65	5.04 5.00	15.02 14.88)
35	1-(m-chlorophenyl)-3-N-n-butylcarbamoyl-5-methoxypyrazole	Colorless Oil	–	b.p. 215/1 mmHg	$C_{15}H_{18}O_2N_3Cl$ (307.8)	58.54 (58.71	5.89 5.96	13.65 13.52)
36	1-(m-chlorophenyl)-3-N-(2'-hydroxyethyl)-carbamoyl-5-methoxypyrazole	Colorless Needles	Ethanol-Petroleum ether	143–145	$C_{13}H_{14}O_3N_3Cl$ (295.7)	52.80 (52.93	4.77 4.81	14.21 14.20)
37	1-(m-chlorophenyl)-3-N,N-diethylcarbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	76–77	$C_{15}H_{18}O_2N_3Cl$ (307.8)	58.54 (58.67	5.89 5.87	13.65 13.59)
38	1-(m-chlorophenyl)-3-N-methyl-N-(2'-hydroxyethyl)-carbamoyl-5-methoxypyrazole	Colorless Oil	–		$C_{14}H_{16}O_3N_3Cl$ (309.8)	54.29 (54.17	5.21 5.30	13.57 13.39)
39	1-(m-chlorophenyl)-3-(piperidin-1-yl)-carbonyl-5-methoxypyrazole	Colorless Oil	–	b.p. 215/5 mmHg	$C_{16}H_{18}O_2N_3Cl$ (319.8)	60.09 (60.26	5.67 5.59	13.14 13.06)
40	1-(m-chlorophenyl)-3-N-(N',N'-diethylaminoethyl)-carbamoyl-5-n-butoxypyrazole oxalate	Colorless Crystalline Powder	Methanol-Petroleum ether	130–132	$C_{20}H_{29}O_2N_4Cl.C_2H_2O_4$ (483.0)	54.71 (54.89	6.47 6.62	11.60 11.38)
41	1-(m-chlorophenyl)-3-N-(N',N'-diethylaminoethyl)-carbamoyl-5-methoxypyrazole oxalate	Colorless Crystalline Powder	Methanol-Petroleum ether	141–143	$C_{17}H_{23}O_2N_4Cl.C_2O_4H_2$ (440.9)	51.76 (51.62	5.72 5.76	12.71 12.54)

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. (Found) C	H	N
42	1-(p-chlorophenyl)-3-N-(N',N'-diethylaminoethyl)-carbamoyl-5-methoxypyrazole oxalate dihydrate	Colorless Crystalline Powder	Methanol-Ethyl acetate	170–171 (decomposition)	$C_{17}H_{23}O_3N_4Cl \cdot 2H_2O \cdot C_2H_2O_4$ (476.9)	47.85 (48.06	6.13 6.15	11.75 11.64)
43	1-(m-nitrophenyl)-3-N,N-dimethylcarbamoyl-5-methoxypyrazole	Colorless Needles	Hydrated acetone	147–148	$C_{13}H_{14}O_4N_4$ (290.3)	53.79 (53.92	4.86 4.73	19.30 19.31)
44	1-(m-aminophenyl)-3-N,N-dimethylcarbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl acetate	118–119	$C_{13}H_{16}O_2N_3$ (260.3)	59.99 (60.18	6.20 6.04	21.52 21.36)
45	1-(p-chlorobenzyl)-3-N-methylcarbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	93–95	$C_{13}H_{14}O_2N_3Cl$ (279.7)	55.82 (55.95	5.04 5.13	15.02 15.01)
46	1-(p-chlorobenzyl)-3-N-sec-butylcarbamoyl-5-methoxypyrazole	Colorless Granules	Ethyl ether-Petroleum ether	63–64	$C_{16}H_{20}O_2N_3Cl$ (321.8)	59.72 (59.93	6.26 6.35	13.06 12.92)
47	1-(3,4-dichlorophenyl)-3-N,N-dimethylcarbamoyl-5-methoxypyrazole	Colorless Needles	Hydrated Methanol	107–108	$C_{13}H_{13}O_2N_3Cl_2$ (314.2)	49.70 (49.78	4.17 4.15	13.37 13.24)
48	1-(3,4-dichlorophenyl)-3-N-(N',N'-diethylaminoethyl)-carbamoyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	64–65	$C_{17}H_{22}O_2N_4Cl_2$ (385.3)	53.00 (52.94	5.76 5.70	14.54 14.68)
49	1-(p-chlorobenzyl)-3-N,N-dimethylcarbamoyl-5-methoxypyrazole	Colorless Flakes	Isopropyl ether-Petroleum benzine	70–71	$C_{14}H_{16}O_2N_3Cl$ (293.8)	57.24 (57.37	5.49 5.52	14.30 14.21)

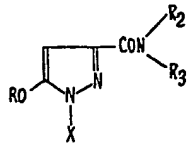
Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. (Found) C	H	N
50	1-(p-chlorobenzyl)-3-morpholinocarbonyl-5-methoxypyrazole	Colorless Needles	Ligroin	115–117	$C_{16}H_{18}C_3N_3Cl$ (335.8)	57.23 (57.38	5.40 5.32	12.51 12.29)
51	1-(p-chlorobenzyl)-3-N-n-butylcarbamoyl-5-methoxypyrazole	Colorless to Pale Yellow Oil	–	b.p. 248/6 mmHg	$C_{16}H_{20}O_2N_3Cl$ (321.8)	59.72 (59.93	6.26 6.37	13.06 12.88)
52	1-(p-chlorobenzyl)-3-N,N-diisopropylcarbamoyl-5-methoxypyrazole	Colorless Prisms	Ethyl ether-Petroleum ether	89–90	$C_{18}H_{24}O_2N_3Cl$ (349.9)	61.80 (61.63	6.91 6.92	12.01 11.86)
53	1-(p-chlorobenzyl)-3-(pyrrolidin-1-yl)-carbonyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	97–99	$C_{16}H_{18}O_2N_3Cl$ (319.8)	60.09 (60.26	5.67 5.67	13.14 13.12)
54	1-(p-chlorobenzyl)-3-carbamoyl-5-methoxypyrazole	Colorless Plates	Ethyl acetate	144–146	$C_{12}H_{12}O_2N_3Cl$ (265.7)	54.25 (54.38	4.55 4.62	15.81 15.68)
55	1-(p-chlorobenzyl)-3-N-(N',N'-diethylaminoethyl)-carbamoyl-5-methoxypyrazole oxalate	Colorless Crystalline Powder	Ethanol-Ethyl ether	155–157 (decomposition)	$C_{18}H_{25}O_2N_4Cl.C_2H_2O_4$ (454.9)	52.81 (52.58	5.98 6.12	12.32 12.16)
56	1-(p-chlorobenzyl)-3-N-methylcarbamoyl-5-n-butoxypyrazole	Colorless Flakes	Methanol-Petroleum ether	124–125	$C_{16}H_{20}O_2N_3Cl$ (321.8)	59.72 (59.68	6.26 6.30	13.06 13.22)
57	1-(p-chlorobenzyl)-3-N-n-butylcarbamoyl-5-n-butoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	70–71	$C_{19}H_{26}O_2N_3Cl$ (363.9)	62.71 (62.88	7.20 7.28	11.55 11.36)
58	1-(p-chlorobenzyl)-3-N,N-dimethylcarbamoyl-5-n-butoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	60–61	$C_{17}H_{24}O_2N_3Cl$ (335.8)	60.80 (60.87	6.60 6.59	12.51 12.37)

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M W.)	Analysis (%) Calcd. (Found) C	H	N
59	1-(p-chlorobenzyl)-3-morpholino-carbonyl-5-n-butoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	85–86	$C_{19}H_{24}O_3N_3Cl$ (377.9)	60.39 (60.53	6.40 6.28	11.12 11.15)
60	1-(p-chlorobenzyl)-3-N,N-di-isopropylcarbamoyl-5-n-butoxy-pyrazole	Colorless Granules	Ethyl ether-Petroleum ether	73–74	$C_{21}H_{30}O_2N_3Cl$ (391.9)	64.35 (64.38	7.72 7.63	10.72 10.59)
61	1-(p-chlorobenzyl)-3-(pyrrolidin-1-yl)-carbonyl-5-n-butoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	86–87	$C_{19}H_{24}O_2N_4Cl$ (361.9)	63.06 (63.27	6.68 6.67	11.61 11.59)
62	1-(p-chlorobenzyl)-3-N-(N',N'-diethylaminoethyl)-carbamoyl-5-n-butoxypyrazole oxalate	Colorless Crystalline Powder	Ethanol-Ethyl ether	138–140	$C_{21}H_{31}O_2N_4Cl.C_2H_2O_4$ (497.0)	55.59 (55.76	6.69 6.73	11.27 11.11)
63	1-(p-chlorobenzyl)-3-(4'-methyl-piperazinyl)-carbonyl-5-n-butoxypyrazole	Colorless Needles	Acetone-Petroleum ether	92–93.5	$C_{20}H_{27}O_2N_4Cl$ (390.9)	61.45 (61.62	6.96 6.85	14.33 14.26)
64	1-(o-chlorobenzyl)-3-carbamoyl-5-methoxypyrazole	Colorless Needles	Hydrated ethanol	163–164	$C_{12}H_{12}O_2N_3Cl$ (265.7)	54.25 (54.29	4.55 4.48	15.81 15.73)
65	1-(o-chlorobenzyl)-3-N-methyl-carbamoyl-5-methoxypyrazole	Colorless Needles	Ethanol-Petroleum ether	131–132	$C_{13}H_{14}O_2N_3Cl$ (279.7)	55.82 (55.98	5.04 5.05	15.02 15.00)
66	1-(o-chlorobenzyl)-3-N,N-dimethyl-carbamoyl-5-methoxypyrazole	Colorless Needles	Ethanol-Petroleum ether	135–136	$C_{14}H_{16}O_2N_3Cl$ (293.8)	57.24 (57.41	5.49 5.46	14.30 13.36)
67	1-(o-chlorobenzyl)-3-N,N-di-isopropylcarbamoyl-5-methoxy-pyrazole	Colorless Prisms	Ethanol-Petroleum ether	130–131	$C_{18}H_{24}O_2N_3Cl$ (349.9)	61.80 (61.72	6.91 6.97	12.01 11.82)

Example No.	Compound	Crystal form	Recrystallization solvent	Melting point	Empirical formula (M. W.)	Analysis (%) Calcd. C	Analysis (%) Calcd. H	Analysis (%) Calcd. N	Analysis (%) (Found) C	Analysis (%) (Found) H	Analysis (%) (Found) N
68	1-(o-chlorobenzyl)-3-(4'-methyl-piperazinyl)-carbonyl-5-methoxy-pyrazole	Colorless Prisms	Ethanol-Petroleum ether	91–92	$C_{17}H_{21}O_2N_4Cl$ (348.8)	58.53	6.07	16.06	(58.69	6.13	15.93)
69	1-(m-bromophenyl)-3-carbamoyl-5-methoxypyrazole	Colorless Needles	Hydrated Methanol	159–161	$C_{11}H_{10}O_2N_3Br$ (296.1)	44.62	3.40	14.19	(44.63	3.41	14.13)
70	1-(m-bromophenyl)-3-N-methyl-carbamoyl-5-methoxypyrazole	Colorless Prisms	Ethyl ether-Petroleum ether	109–110	$C_{12}H_{12}O_2N_3Br$ (310.2)	46.47	3.90	13.55	(46.61	3.83	13.32)
71	1-(m-bromophenyl)-3-N-ethyl-carbamoyl-5-methoxypyrazole	Colorless Prisms	Ethyl ether-Petroleum ether	80–81	$C_{13}H_{14}O_2N_3Br$ (324.2)	48.17	4.35	12.96	(48.25	4.23	12.78)
72	1-(m-bromophenyl)-3-N,N-dimethyl-carbamoyl-5-methoxypyrazole	Colorless Prisms	Hydrated Methanol	88–89	$C_{13}H_{14}O_2N_3Br$ (324.2)	48.17	4.35	12.96	(48.10	4.31	12.91)
73	1-(p-methoxyphenyl)-3-N,N-dimethylcarbamoyl-5-methoxy-pyrazole	Colorless Prisms	Ethanol-Petroleum ether	112–113.5	$C_{14}H_{17}O_3N_3$ (275.3)	61.08	6.22	15.26	(60.95	6.18	15.18)
74	1-(p-methoxyphenyl)-3-morpholino-carbonyl-5-methoxypyrazole	Colorless Needles	Ethyl ether-Petroleum ether	86–87	$C_{16}H_{19}O_4N_3$ (317.3)	60.56	6.03	13.24	(60.59	5.92	13.10)

WHAT WE CLAIM IS:—

1. Pyrazole derivatives represented by the formula



(I)

wherein R represents an alkyl group, X represents a mono- or di-substituted phenyl group wherein the substituents may be the same or different and each represents an alkyl group, an alkoxy group, a trifluoromethyl group, a nitro group, an amino group or a halogen atom; or a substituted or unsubstituted benzyl group wherein the substituent is a halogen atom, R_2 represents a hydrogen atom or an alkyl group and R_3 represents a hydrogen atom, a hydroxyalkyl group, an alkyl group or a substituted aminoalkyl group, or R_2 and R_3 may form, when taken together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic group which may contain one oxygen as a hetero atom; and acid addition salts thereof.

2. 1 - (p - Tolyl) - 3 - N,N - dimethylcarbamoyl-5-methoxypyrazole.

3. 1 - (m - Trifluoromethylphenyl) - 3-N,N - dimethylcarbamoyl - 5 - n - butoxypyrazole.

4. 1 - (m - Chlorophenyl) - 3 - N,N-dimethylcarbamoyl-5-methoxypyrazole.

5. 1 - (m - Chlorophenyl) - 3 - carbamoyl-5-methoxypyrazole.

6. 1 - (p - Chlorobenzyl) - 3 - N - methylcarbamoyl-5-methoxypyrazole.

7. 1 - (m - Chlorophenyl) - 3 - N-methylcarbamoyl-5-methoxypyrazole.

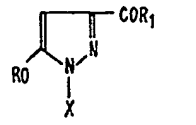
8. 1 - (m - Chlorophenyl) - 3 - N - ethylcarbamoyl-5-methoxypyrazole.

9. 1 - (m - Bromophenyl) - 3 - N - methylcarbamoyl-5-methoxypyrazole.

10. 1 - (m - Bromophenyl) - 3 - N-ethylcarbamoyl-5-methoxypyrazole.

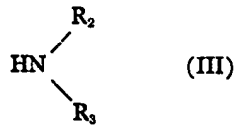
11. 1 - (m - Bromophenyl) - 3 - N,N-dimethylcarbamoyl-5-methoxypyrazole.

12. A process for preparing a pyrazole derivative represented by the formula (I) as defined in Claim 1, which comprises reacting 5-alkoxypyrazole represented by the formula



(II)

wherein R and X are as defined above, and R_1 represents an alkoxy group, a hydroxy group or a halogen atom, with an amine represented by the formula



(III)

wherein R_2 and R_3 are as defined above, in an inert organic solvent or in the presence of an excess of said amine.

13. A process according to Claim 12, wherein (II) and (III) are reacted at a temperature of from 0° C to 80° C using at least an equimolar amount of said amine relative to said 5-alkoxypyrazole for a period of from 20 minutes to 16 hours.

14. A process according to Claim 12 or 13, wherein the alkoxypyrazole in which R_1 represents an alkoxy is reacted with said amine in an alkanol having 1 to 4 carbon atoms or benzene in a molar ratio of from 1 to 5 moles of said amine per 1 mole of said 5-alkoxypyrazole at a temperature of from 60 to 80° C for a period of from 1 to 5 hours, optionally in the presence of a condensing agent.

15. A process according to Claim 14, wherein said condensing agent is aluminium isopropoxide or sodium amide.

16. A process according to Claim 12 or 13, wherein the 5-alkoxypyrazole in which R_1 represents a halogen atom is reacted in an inert organic solvent selected from ethyl ether, chloroform, benzene, pyridine and triethylamine for a period of from 20 minutes to 2 hours.

17. A process according to Claim 12 or 13, wherein the 5-alkoxypyrazole in which R_1 represents a hydroxy group is reacted with said amine in an inert organic solvent which is methylene chloride or chloroform for a period of from 3 to 16 hours, optionally in the presence of a dehydrating agent.

18. A process according to any one of Claims wherein the pyrazole is subsequently converted to an acid addition salt.

19. A process according to Claim 12 or 18 and substantially as hereinbefore described.

20. A process for preparing a pyrazole derivative of the general formula defined in Claim 1 or an acid addition salt thereof, substantially as herein described with reference to any one of Examples 1 to 74.

21. A pyrazole of the general formula defined in Claim 1 or an acid addition salt thereof, when prepared by a process as claimed in any one of Claims 12 to 20.

22. A pyrazole or an acid addition salt thereof being any one of the compounds described herein as the product of Examples 1 to 74.

23. A pharmaceutical composition comprising a pyrazole as claimed in any one of Claims 1 to 11, 21 and 22 or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

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